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Autonomous hypercortisolism: definition and clinical implications

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ABSTRACT

In current practice, an adrenal adenoma usually comes as an unexpected byproduct of an imaging study performed for unrelated reasons, without any prior suspect of adrenal disease. Therefore, these tumors currently represent a public health challenge because they are increasingly recognized due to the widespread use of high-resolution cross-sectional imaging for diagnostic purposes. In radiology series, the prevalence of adrenal adenomas increases steeply with age, from around 3% below the age of 50 years up to 10% in the ageing population. These tumors may have clinical relevance because they are able to secrete cortisol autonomously, independently from the pituitary control, in up to 20% - 30% of patients. In most of the cases the resulting cortisol excess is insufficient to produce a typical Cushing phenotype but may have clinical consequences, such as hypertension, diabetes, obesity, dyslipidemia and osteoporosis.

Despite some controversy on the most effective diagnostic algorithm to define this subtle hypercortisolism, there is mounting evidence that a simple approach by using the 1-mg overnight dexamethasone suppression test (DST) may stratify patients for their cardiovascular risk. Cross-sectional, retrospective studies showed that patients with increasingly higher cortisol following DST have an adverse cardiovascular risk profile and are at increased risk of death. Therefore, also a subtle autonomous cortisol excess is associated with increased morbidity and mortality, mainly of cardiovascular origin.

KEY WORDS

Adrenal adenoma

Hypercortisolism

Cushing's syndrome

INTRODUCTION

Adrenal adenomas are benign tumors with a limited potential of malignant transformation. In current practice, an adrenal adenoma usually comes as an unexpected byproduct of an imaging study performed for unrelated reasons, without any prior suspect of adrenal disease. Therefore, they currently represent a public health challenge because they are increasingly recognized due to the widespread use of high-resolution cross-sectional imaging for diagnostic purposes.

These tumors may have clinical relevance because they are able to secrete cortisol autonomously, independently from the pituitary control, in up to 20% - 30% of patients[1]. In most of the cases the resulting ACTH-independent cortisol excess is mild and insufficient to produce a typical Cushing phenotype (facial plethora, easy bruising, proximal muscle weakness, purple striae or weight gain with decreasing growth velocity). Considering the lack of classical external features of Cushing's syndrome (CS), this condition has been defined as subclinical Cushing's syndrome (SCS)[2] (Table I). When adrenal adenomas are associated with highly predictive features of CS[3], the ACTH-independent cortisol excess is usually promptly recognized. However, endogenous hypercortisolism is a rare disease with an estimated incidence of around 2.4 per million and a prevalence of 39.1 per million[4] and ACTH-independent cortisol excess due to adrenal adenoma represents only 10% of the overall causes. On the contrary, the epidemiologic relevance of SCS due to adrenal incidentalomas is potentially high, considering that in radiology series the prevalence of adrenal adenomas is around 3% below the age of 50 years, with progressive increase in older patients (up to 10% in the ageing population)[1] and in approximately 20-25% of them an autonomous cortisol secretion is reported.

However, the demonstration of autonomous cortisol secretion could be extremely difficult in practice. The heterogeneity of clinical phenotype and a limited clinical experience make precocious diagnosis a major challenge and frequently SCS remain unrecognized for long time, due its subtle course. In the meanwhile, patients exposed to chronic albeit slight cortisol excess may have significant clinical consequence, such as hypertension, diabetes, obesity, dyslipidemia and osteoporosis.

DEFINITION OF AUTONOMOUS ACTH-INDEPENDENT HYPERCORTISOLISM

According to the Endocrine Society guidelines[3], overt endogenous hypercortisolism should be investigated when clinical features and history are highly predictive. The recommended screening evaluation includes the following test: 1 mg overnight dexamethasone suppression test, urinary free cortisol (UFC) and late night salivary cortisol. When at least two of them are positive, the diagnosis is confirmed. If an adrenal adenoma is detected by radiological imaging, the diagnosis of ACTH-independent CS requires low ACTH levels (<1.1 pmol/L). This two-step diagnostic procedure is highly effective in presence of high clinical pre-test probability. However, most of the patients may

present a mild disease, that is harder to detect. Thus, several studies have been focused on such patients with diabetes mellitus, osteoporosis, hypertension or obesity to screen for mild hypercortisolism. Although a widespread screening is not recommended, interestingly most of the detected cases with confirmed hypercortisolism had an adrenal dependent CS [5-7].

According to the ESE guidelines[1], the best method to discover autonomous cortisol secretion is the 1 mg overnight dexamethasone suppression test (1 mg-DST). Nevertheless, false positive or false negative results are reported, mainly due to variable absorption and metabolism of dexamethasone[3]. Many drugs cause false positive results, as phenytoin, increasing hepatic metabolism of dexamethasone mediated by CYP3A4 (phenobarbitone, carbamazepine or rifampicin) or raising CBG levels (oral estroprogestinic preparations). On the contrary, false negative results could be due to liver or renal failure, which reduce dexamethasone clearance.

Twenty-four hour UFC is widely used in the clinical practice, but considering that it reflects the measure of cortisol circulating levels after CBG saturation, it is less sensitive in patients with mild hypercortisolism or in patients with AI. Moreover, several limits have been reported due to the need of multiple collection, improper collection, high fluid intake or renal insufficiency [8-10].

Although the LC-MS / MS technique is not available in all centers, it appears promising to improve diagnostic accuracy, since interference with other steroids is excluded. Therefore, it is the recommended technique for the evaluation of UFC as first-line screening of CS[3] and recent studies have confirmed higher sensitivity and specificity of UFC with LC-MS / MS [11,12].

The evaluation of the circadian rhythm of cortisol is one of the most important diagnostic clue since the loss of the ultradian pulsatility of cortisol secretion with high nocturnal values is pathognomonic of cortisol excess. However, methodological limits, in addition to the non-uniformity of pathological thresholds, make the consent difficult and the use not widespread, especially for mild hypercortisolism.

Newell-Price and colleagues[13] first suggested the use of midnight serum cortisol as a screening test, and in recent years its higher sensitivity and specificity was reported [14,15]. Moreover, the midnight serum cortisol threshold of 148 nmol/L has been also documented to be related with an adverse cardiovascular (CV) risk profile in patients with AI[16]. However, it requires hospitalization and cannot be proposed for routine clinical practice.

The introduction of midnight salivary cortisol has avoided hospitalization and has become one of the most important diagnostic tools in CS. A meta-analysis demonstrated an overall sensitivity of 92% and a specificity of 96%, although there is no agreement on the definition of the cut-off and it is necessary to define the levels of normality in each laboratory [17, 18]. Only few studies have verified the diagnostic accuracy of salivary cortisol at midnight in subclinical hypercortisolism with results that

are mostly lower than other tests. Recently, data published by Ceccato and colleagues [19] have confirmed the reduced accuracy of midnight salivary cortisol in the screening of subclinical hypercortisolism, although measured by LC-MS/MS. Furthermore, it has not been shown to be a strong predictor of accelerated atherosclerosis in patients with subclinical hypercortisolism [20].

Although low ACTH concentrations may support diagnosis of cortisol autonomous hypersecretion, in some cases non-suppressed ACTH levels are associated with pathological value of 1 mg-DST. A possible explanation can be due to analytical errors or interference in ACTH immunoassay. Particularly, negative impact of antibody interference in ACTH measurements was recently reported in adrenal adenomas incidentally detected[21]. As no single routine test is available to identify immunoassay interference, the same authors suggest to ensure collaboration between clinical and laboratory staff to avoid clinical misjudgments.

The usefulness of DHEAS measurements in the screening of subclinical hypercortisolism is still debated. In the last years DHEAS measurement had a renaissance in this setting also by using LC-MS/MS. Lower DHEAS levels have been confirmed to be correlated to higher cortisol secretion and in some cases with a worsen metabolic profile. However, when compared with the 1 mg DST the sensitivity and specificity in the detection of subclinical hypercortisolism ranges between 70-75% [22,23]. More recently data on 185 patients with AI, of which 29 with subclinical hypercortisolism, DHEAS measurements calculated as age- and sex-specific DHEAS ratios for all patients (derived by dividing the DHEAS by the lower limit of the respective reference range) seem to demonstrate that a single basal measurement of DHEAS offers comparable sensitivity and greater specificity to the existing gold-standard 1 mg DST for the detection of SCS in patients with AI [24].

In conclusion, despite some controversies, use of the 1-mg DST as screening test meets the recent spending-review policies of healthcare systems and limit false positive results. Moreover, there is mounting evidence that the 1-mg DST is useful to stratify patients for their CV and metabolic risk.

Indeed, it has been demonstrated that patients with impaired suppression of cortisol after 1 mg dexamethasone test have a higher risk of type 2 diabetes mellitus (T2D), hypertension, CV events and vertebral fractures.

Urine steroid metabolomics analysis should be a prospective and promising technique to differentiate secreting and non secreting adrenal tumors.

MORBIDITY AND MORTALITY IN ADRENAL-DEPENDENT CUSHING'S SYNDROME (ACS)

The effects of hypercortisolism on morbidity and mortality have been extensively studied, but most published papers have focused on patients with Cushing's disease (CD) and fewer on patients with ACS. It is evident that the therapeutic approach to patients with CD is more complex and often requires different and sequential treatments with a persistent risk of hypercortisolism which is maintained for longer periods. As for patients with ACS, the therapeutic approach is by definition surgical and, in absence of clinical contraindications that determine a high operative risk, it results definitive obtaining the cure in 100% of the cases, although the negative effects of pre-surgical hypercortisolism cannot be removed. In this clinical context, however, post-surgical hypoadrenalism, often prolonged, must be considered until it becomes definitive and potentially influences the quality of life and the clinical management of patients who are on steroid replacement therapy.

METABOLIC AND CARDIOVASCULAR MORBIDITY

Impaired glucose tolerance, hypertension, CV disease and thromboembolism are very common features of CS and frequently reported as risk factors of mortality [25]

It is known that patients with CS showed abdominal obesity (37–71%) and dyslipidemia (hypercholesterolemia in 16–60% and hypertriglyceridemia in 7–36%)[26]. This pattern is due to differential effects of GCs on visceral and peripheral adipose tissues. Indeed, the GC excess induces lipogenesis in visceral fat, whereas in peripheral fat it promotes lipolysis[27]. Moreover, hypercortisolism induces abnormalities in glucose homeostasis, mainly caused by insulin resistance and impairment in insulin secretion, which may persist even after correction of glucocorticoid excess [28].

In addition to metabolic changes, patients with CS are frequently affected by hypertension (55-85%), coagulopathy, structural cardiac alterations (in 70% of cases abnormal left ventricular (LV) mass, with concentric hypertrophy or concentric remodelling) and endothelial dysfunction [26].

Recently, new mechanisms are reported to explain the high CV risk in CS patients.

In 2015, Boero and colleagues carried out an open cross-sectional study to identify the presence of atherogenic risk factors in 32 patients with active CS compared with sex- and age-matched controls. Patients with CS showed lower insulin sensitivity, higher waist circumference, high oxidized low-density lipoprotein levels, high sensitive C-reactive protein levels and increased leukocyte count [29].

Moreover, in 2017, Gokosmanog and colleagues analyzed prevalence of obstructive sleep apnea (OSA) in 30 female patients with active CS and 30 matched healthy controls. They reported higher prevalence of OSA in patients with CS compared with control subjects with similar ages and BMI levels, identifying hypercortisolemia as an independent risk factor for OSA [30].

This multifactorial and variegated pathogenesis of CV morbidity in CS is summarized in Fig 1. However, data focused on adrenal-dependent CS are few and mostly collected aiming to evaluate the efficacy of treatment. At diagnosis, the prevalence of CV risk factors in patients with ACS seems to be similar to CD [31], and higher than in BMI-matched controls [32].

On the other hand, controversial data are available on the effect of therapy in reducing CV risk factors. When studies are predominantly focused on patients with CD, disease remission appears to have only a moderately positive effect over the long term, while maintaining a higher risk compared to the general population [33-34].

Although the risk of CV events is not completely eliminated, studies that include patients in remission with ACS demonstrate more successful results. Giordano and colleagues showed that a significant reduction in impaired glucose tolerance was achieved only in patients with ACS after only one year follow-up[32]. A recent study by Terzolo and colleagues has demonstrated, over a long period of follow-up a complete normalization of CV risk factors in a higher percentage of patients compared to previous publications, having included patients who had already completed the steroid replacement therapy, which had an average duration of about 12 months. In other studies, some patients in remission had ongoing replacement therapy and the possible effect on CV risk outcomes should not be excluded, although further data are needed [35].

OSTEOPOROSIS AND FRACTURE RISK

Osteoporosis is widely documented and up to 80% of patients with CS are reported with an associated risk of fractures exceeding 50% [25]. Moreover, unexpected osteroporosis for patient's age or the rapid worsening of bone mineral density, represent relevant signs of CS. Osteoporosis and fracture risk has been well studied in the different etiologies of Cushing following the hypothesis that the suppression of androgens in patients with ACS could determine a reduction of their protective effect on bone mass favoring the negative effect of excess cortisol. Some works have confirmed this hypothesis, demonstrating a correlation between DHEAS levels and bone mineral density [36, 37], while others did not highlight differences between etiologies [38, 39]. It is likely that the controversial data depend on the different selection of patients, in particular regarding the gonadal status and the hormonal replacement therapy in patients with post-surgical pituitary deficiency.

OTHER MORBIDITIES

GC excess is associated with neuropsychiatric diseases, probably due to structural and functional changes in brain areas expressing GC receptors, such as the hippocampus, amygdala, and anterior cingulated cortex (limbic system, involved in emotional and cognitive attitudes). Particularly, in

patients with CS is reported an high prevalence of major depression (50–81%), anxiety (66%), and bipolar disorders (30%)[40]. It is worth of note that cognitive, psychiatric and mood disorders may persist also after resolution of cortisol excess, with a significant impact on quality of life [41].

Moreover, hypercortisolism impairs the immune system, causing immunosuppression and, consequently, susceptibility to infections (especially due to opportunistic pathogens). Interestingly, the increase risk of invasive infections appears to be independent of the etiology of CS, but is correlated with the severity of GC excess and the success in treatment of opportunistic infections frequently depends on the rapidity in normalizing cortisol levels [25].

MORTALITY

Several data have been published in the last decade on mortality in patients with endogenous hypercortisolism confirming the expected excess compared to the general population, mainly due to cardio- and cerebro-vascular events or sepsis. The excessive mortality is described in patients with persistent disease, while patients in remission may have a comparable risk to the general population or at least only a slight increase [25].

The investigation of the Standard mortality ratio only in patients with adrenal-dependent benign unilateral adrenal adenoma vary greatly from 1.35 to 7.5 [42-46]. However, recent data from two large series with a prolonged follow-up reported that patients in remission with ACS does not have an excess risk mortality compared to the general population and it is similar or slightly lower than patients with CD [45, 46].

MORBIDITY AND MORTALITY IN SUBCLINICAL CUSHING SYNDROME (SCS)

An increasing body of evidence suggests association between SCS and metabolic alterations, CV disease and osteoporosis. Long-term exposure to even low-grade cortisol excess may have detrimental effects depending on individual genetic background, associated clinical conditions and degree of hypercortisolism. Moreover, recent studies showed higher mortality in this group of subjects.

METABOLIC AND CARDIOVASCULAR MORBIDITY

It is known the effect of glucocorticoids on glucose metabolism, including increase of hepatic gluconeogenesis, decrease of insulin-dependent glucose uptake in peripheral tissues and inhibition of insulin secretion from pancreatic β-cells[47]. Therefore, it is not surprising the association between SCS

and impairment of glucose metabolism, including insulin resistance, impaired glucose tolerance (IGT) and T2M. High prevalence of IGT (36%) or previously undiagnosed T2M (5%) has been described since 2002[48] in patients with AI in comparison with controls. Moreover, the same authors reported higher levels of 2-h glucose after oral glucose tolerance test (OGTT) ($p = 0.03$) and reduced insulin sensitivity index (ISI) ($p < 0.0001$) in the subgroup of patients with adrenal adenoma and SCS compared to subgroup of patients with nonfunctioning adenoma. In the following years, several studies have been conducted in this field and it has been reported T2D roughly in one third of patients with SCS, but with a broad range from 5% to 69%[49]. This variability could depend on different diagnostic criteria used to define SCS, number of examined patients and different method used to evaluate the presence of glucose metabolism impairment. Particularly, it is worth of note that assessment of fasting glucose and fasting insulin in SCS is not sufficient to detect glucose metabolism impairment and an OGTT is required[50]. Due to similar reasons (variability of diagnostic cut-off for SCS), the reported prevalence of mild hypercortisolism in cohorts of patients with T2D is extremely variable. In 2003 Catargi and colleagues described a 3.5% prevalence of SCS in a population of 200 diabetic patients[51], while in 2005 Chiodini and collegaues[52] reported a rough prevalence of 7%, 4.8-fold higher than in non-diabetic group, independently of potentially confounding comorbidities as obesity and hypertension. More recently, a large single center study, conducted in a cohort of 993 Asian Indian patients with T2D[53], reported in 37 cases (3.72%) a value of cortisol after 1-mg DST > 50 nmol/L. These patients have been further evaluated with a 48 h, 2 mg low dose DST (LDDST) after a gap of at least 1 week after 1-mg DST and none of them had cortisol >50 nmol/L, nor did they develop clinically evident CS over a follow-up period of 1 year. Only on the basis of these biochemical and clinical data, the Authors concluded that none of the T2DM patients in their cohort had SCS. Conversely, Costa and colleagues[54] reported, in a large sample of T2D patients with high CV risk, a prevalence of 8.6% of SCS. Moreover, these patients had more severe hypertension and increased aortic stiffness, despite of a shorter diabetes duration. Regardless this variability of findings, currently it is suggested against systematic biochemical screening for SCS in T2D cohort, while diagnostic investigations should be reserved for cases of clinical suspicion. On the contrary, SCS patients had to be screened for T2D [1]. Although less proven, association with dyslipidemia is also plausible. Interestingly, Masserini and colleagues showed that in absence of impaired glucose metabolism a mild hypercortisolism has no effect on lipid pattern[55]. Finally, recent studies showed that patients with SCS have a high prevalence of nonalcoholic fatty liver disease[56] and visceral fat accumulation (measured by CT-scan)[57].

An increased CV risk profile in SCS subjects was first demonstrated in 2002, with a cross-sectional study including 28 SCS patients compared with 100 controls. Systolic and diastolic blood pressures,

fasting glucose, insulin, total cholesterol, triglycerides, fibrinogen were higher in SCS patients, as were insulin resistance index, waist to hip ratio, mean carotid artery intima-media thickness and prevalence of atherosclerotic plaques. Moreover, among SCS patients it was reported a symptomatic CV disease in six subjects (21.3%) and CV abnormalities (revealed by ultrasound scanning of carotid arteries and/or electrocardiogram records) in 11 cases (39.3%)[58]. In 2005 a multicenter retrospective study including 210 patients with clinically inapparent adrenal adenoma reported higher fasting glucose and systolic blood pressure in patients with elevated midnight serum cortisol concentrations compared to subjects with normal cortisol levels[16]. A significance contribute was also provided by a cross-sectional study published in 2012, including 348 patients with AI, classified in 4 subgroups: 203 patients with non-secreting adenoma (NSA, with 1 mg DST < 50 nmol/l), 19 patients with SCS (1 mg DST >138 nmol/l) and the remaining patients with intermediate phenotype (1 mg DST between 50 and 138 nmol/l), divided in minor (71 patients) or major (55 patients) according plasma ACTH and/or UFC levels. It is worth of note the increase of prevalence of myocardial infarction according to secreting pattern (2.9% in NSA, 11.9% in patients with intermediate phenotype and 26.3% in SCS). Moreover, multivariate logistic regression analysis showed association between prevalence of coronary heart disease and patients with intermediate phenotype or SCS, independently of other potential risk factors[59]. These important findings were confirmed by the same authors in a retrospective analysis of 198 patients, evaluated for their cortisol secreting pattern at baseline and at the last visit, with a mean follow-up of 7.5±3.2 years (range 26 months - 15 years). It was reported that patients with SCS and with worsening cortisol secretion at the last visit (compared to baseline) had higher incidence of CV disease than those with NSA. Moreover, increase of cortisol levels during follow-up was independently associated with higher rate of CV events[60]. Finally, the role of cortisol as a contributing factor to CV diseases was confirmed in other retrospective studies, reporting higher incidence of CV events in patients with SCS than in patients with NSA[61-63].

More recently Arruda and colleagues, reported the association between hypertension and cortisol levels after 1 mg-DST in patients with NSA[64]. Although there is no indication to a routine screening for cortisol secretion in patients with hypertension, the high prevalence of SCS shown in patients with resistant hypertension, associated with several markers of worse CV prognosis[65] probably needs further assessments.

OSTEOPOROSIS AND FRACTURE RISK

In the last decade, several studies investigated the impact of mild hypercortisolism on bone healthy. Retrospective series[66-69] reported increased prevalence of bone fractures, mainly in trabecular bone, in patients with SCS compared to patients with NSA or healthy subjects.

In 2011 a first longitudinal study confirmed higher prevalence of vertebral fractures and also reported, using the surrogate tool of spinal deformity index (SDI), worsened bone quality in SCS patients in comparison to patients with AI. Moreover, it was showed that SCS patients had higher risk to develop new vertebral fractures over time despite a stable bone mineral density (BMD)[70].

Deterioration of bone quality in SCS patients was confirmed in a subsequent prospective study, in which trabecular bone score (TBS) was used as surrogate index of damaged bone microarchitecture. It was found that TBS was inversely correlated with 1-mg DST regardless of age, BMD, body mass index (BMI) and gender. Moreover, in patients with SCS, the presence of fractures was associated with low TBS, and its value predicted occurrence of new microfractures, regardless of BMD[71].

Correlation between mild hypercortisolism and bone quality was further investigated in OsteoLaus cohort, including 608 women >50 years old, in which salivary cortisol circadian rhythm was assessed. Lower TBS values ($p = 0.02$), more vertebral fractures ($p = 0.012$) and major osteoporotic fractures ($p = 0.042$) were reported in women with 8 PM salivary cortisol in the highest tertile compared to women with salivary cortisol in lowest tertile, without difference in lumbar spine BMD[72].

In a recent study including 110 patients with overt Cushing (OC: UFC > 1.5 ULN and 1 mg DST > 50 nmol/L) or mild autonomous cortisol secretion (MACE: normal UFC associated with 1 mg DST > 50 nmol/L), a group of 29 patients with MACE due to AI was compared with a group 18 patients with NSA (normal UFC associated with 1 mg DST < 50 nmol/L). Patients with MACE had lower TBS than patients with NSA ($p < 0.04$), despite similar BMD, age, BMI and female predominance. Moreover, 52% of patients with MACE and 33% of patients with NSA ($p = 0.05$) had impaired bone microarchitecture (as indicated by their TBS)[73].

MORTALITY

Recent studies have also shown that SCS is associated with an increase in mortality rate. A 15-year retrospective study[60] showed that in 198 patients followed up for a mean 7.5 years 21 patients died, 48% attributable to CV disease and 43% due to cancer. All-cause (57 vs. 91%) and CV specific mortality (78 vs. 98%) survival rate was worse in SCS patients compared with NSA. Another retrospective, longitudinal cohort study[62] involving 206 patients (mean follow-up 4.2±2.3 years), confirmed the relationship between a low-grade excess cortisol and an increased mortality rate. It is worth of note that patients with SCS showed higher mortality rate related to cardiovascular disease and infection when compared with UK population.

CONCLUSION

Since the first years of the new millennium, the growing number of incidentally discovered adrenal

masses increased the interest on their clinical management, primarily in identifying malignancy, but also in demonstrating a potential increase in cortisol secretion and its consequences in patients who did not show any of the typical signs and symptoms of hypercortisolism. While in overt Cushing's syndrome it is clearly demonstrated that associated co-morbidities (CV events, metabolic syndrome, osteoporosis, psychiatric disorders, and infective diseases) contribute to an increase mortality risk, which is not always completely reversible after disease remission, in patients referred to the clinician for incidentally discovered adrenal masses, without any signs and symptoms of hypercortisolism, the diagnostic evaluation and the potential clinical implications were more complex to study and there are still unresolved questions. Although the measure of cortisol after overnight 1 mg DST is currently the most accurate, less expensive and easiest test to identify patients with an autonomous cortisol secretion, there are still areas of uncertainty in patients with cortisol levels higher than 50 nmol/L. The addition of further hormone evaluations does not provide sufficient specificity, thus it is still crucial to identify new diagnostic methods, which allow to better measure the chronic exposure to a slight cortisol excess. The assessment of potential co-morbidities is essential in identifying the best therapeutic approach. Many studies confirm a correlation between a progressive increase of impaired glucose metabolism, CV events and osteoporosis with higher cortisol secretion and early data seem to demonstrate an increasing effect on mortality. Actually, further extensive studies are needed to better discriminate the effect of hypercortisolism, especially in older patients who have an age related co-morbidity risk. The prospective aim will be to accurately identify and to categorize, from the initial clinical and biochemical assessment, patients who can benefit from specific treatments for hypercortisolism.

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Tab I. Relevant differences between Subclinical Cushing Syndrome and Overt Cushing Syndrome.

	SUBCLINICAL CUSHING SYNDROME	OVERT CUSHING SYNDROME
Age at diagnosis	Frequently > 50 years	Frequently < 50 years
Sex	Slight prevalence in women	Clear prevalence in women
Presentation and cause of disease	Usually, adrenal mass incidentally finding during radiological exams, in patients with characteristics of metabolic syndrome,	Clinical suspect on the basis of

	without specific features of Cushing	specific signs of Cushing, followed by radiological exams frequently showing a pituitary adenoma
Disease course	Usually does not progress to overt Cushing's syndrome	Usually progressive to more severe clinical presentation
Prevalence of hypoadrenalism after surgery	Hypoadrenalism may results after removal of adrenal tumor	Hypoadrenalism invariably follow removal of causing tumor

Modified from Terzolo at al.[2]